PESTICIDES

The use of pesticides in the growing and storing of tobacco may result in the detection of very small residual amounts of these substances in tobacco products. Claims have been made that these residues in cigarettes may play a role in the causation of certain diseases. However, no persuasive scientific studies have been reported which establish that the very small amounts of residues that have been detected in cigarette smoke cause disease in smokers.[1-3] Furthermore, extensive government regulation of pesticide use is designed to assure their proper use and application in the growth and cultivation of tobacco.

Pesticides are important agricultural chemicals that are widely used in the production of farm crops throughout the world. The term "pesticide" refers to those chemicals that are formulated and marketed by chemical manufacturers to control a wide range of pests that can cause substantial agricultural production losses. These include insects (insecticides), weeds (herbicides), worms (nematocides), fungi (fungicides), rodents (rodenticides) and other organisms. Accordingly, pesticides make an important contribution to worldwide agricultural success. As a result of approved uses, small amounts of residues from these chemicals are found in virtually all the foods in one's daily diet. Pesticides used in

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growing these food commodities are also used in tobacco agriculture.

Pesticides in Perspective

In order to understand the significance of the small amounts of pesticides reportedly found on agricultural crops, it is important to place pesticides and their residue levels in the proper perspective. A pesticide should not be perceived as a health risk simply because it is synthetic or man-made and has been used in agriculture. The mechanism of action that makes pesticides effective in controlling various pests and weeds does not automatically translate into health concerns or an adverse impact on the environment.

To evaluate the possible effect of small residues of pesticides, one must also consider other sources of chemicals that contribute to the array of substances to which humans are exposed. Even though synthetic pesticides are used all over the world, the major source of pest control chemicals is nature itself. All grain, fruit and vegetable plants are known to produce "pesticides" as chemical defenses to infestation by insects, fungi and animal predators. It has been estimated, for example, that one's diet includes about 1.5 grams of these natural "pesticides" during an average day, an amount which has been calculated to be about 10,000

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times the amount of synthetic pesticide residues consumed. In other words, 99.99% of the pesticides consumed through the diet are naturally-occurring.[4]

Pesticide Residues on Tobacco

In evaluating the claims about pesticide residues in tobacco, as with the potential hazards associated with exposure to any substance, it is necessary to consider the fundamental toxicological concept that "the poison is in the dose."[5,6] Any substance given at a high enough dose is toxic, even oxygen and water. Likewise, any substance given at a dose well below its level of demonstrated toxicity would not be expected to result in toxic effects. The applicability of this concept in evaluating any potential effect of human exposure to the extremely low levels of pesticide residues that may be detectable in tobacco is readily apparent.

Tobacco undergoes substantial transformation from the raw leaf to the manufactured cigarette. The levels of pesticide residues that may be found on raw tobacco at the time of harvest are greatly reduced by the time the tobacco is incorporated into the final product. This transformation from the raw leaf to the cigarette is a result of the curing, aging, blending and manufacturing processes employed to produce a finished product

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acceptable to the consumer. A significant reduction of pesticide residues occurs during curing, aging and blending. Moreover, steam and heat used in the manufacturing process lead to substantial reductions in residue levels. All of these processing steps and the necessary time lapse that occurs, from harvest of the raw tobacco to the final manufactured product, result in extensive dissipation of the residues.

Even the tiny amounts of pesticide residues that may be present in the final cigarette do not represent the amounts, if any, that may ultimately transfer into mainstream smoke. (Mainstream smoke is the smoke that is drawn through the rod of a burning cigarette by the smoker.) For example, residues of maleic hydrazide that may be detectable in cigarettes do not appreciably transfer into mainstream smoke; a mainstream transfer rate of approximately 0.2% has been reported.[7] Not even the United States Surgeon General has claimed that the pesticide residues detectable in cigarettes are a proven health problem.[8,9]

Government Regulation

In many countries, the use of pesticides and the presence of residues in agricultural food commodities are subject to government regulation. These countries have developed pesticide approval standards, based on extensive scientific data, for the

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purpose of ensuring that the regulated pesticide residues do not represent a risk to environment or health. The purpose of such government regulations is to ensure the proper use of approved pesticides to enhance crop production without exposing the farmer, the consumer or the environment to risk. It is the practice of the major tobacco manufacturers to purchase and use only that tobacco grown and sold in accordance with the government regulations applicable in the respective countries.

The extent to which governments regulate pesticides varies from country to country. For example, among the European countries, Germany is noted to have a comprehensive set of pesticide tolerances on tobacco and other crops. Many of its neighbors refer to Germany's regulations to govern pesticide tolerance levels in their own countries. The German regulations specify maximum permitted levels on tobacco for residues of many pesticides; the use of other specified pesticides is also allowed if prescribed agricultural practices are followed and the residues do not exceed a recommended maximum amount. These residue levels are applicable to tobacco after it has been processed into the finished product.[10] Tolerances on tobacco have also been set in a limited number of other countries.[11,12] Between the countries with residue tolerance regulations, there are a number of inconsistencies in the residue levels set for certain pesticides.

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The European Community (EC) is expected to consider the issue of tobacco pesticide regulation and may develop uniform standards by 1992. If the EC adopts a directive for tobacco that establishes standardized tolerances, it may include pesticides currently regulated in Germany and other EC Member States.[12]

In the United States, the use of pesticides on all agricultural products, including tobacco, is approved and otherwise regulated principally by the Environmental Protection Agency (EPA). The U.S. Department of Agriculture (USDA) also has certain regulatory responsibilities in this area.[13] In order for their crops to qualify for the government price support program, U.S. tobacco farmers must certify that they have used only approved pesticides in accordance with specific application requirements.

Advances in Detection of Pesticide Residues

During the last several years, pesticide residues in food and drinking water have been the subject of numerous publications in technical journals and in the lay press. Among the most prominent factors contributing to public awareness on this subject are the tremendous advances in analytical science that have occurred in the last two decades. Technological developments in analytical instrumentation and methodology have made it possible to detect

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extremely small residues of pesticides in a variety of commodities that were virtually undetectable only a few years ago.

It is difficult for the non-scientist to comprehend the significance of chemicals detectable at levels of parts per million, parts per billion and parts per trillion in agricultural products, water supplies and other products intended for human consumption. For example, it is important for the public to understand that one part per million is the equivalent of one second in twelve days or one centimeter in 10.3 kilometers (one inch in sixteen miles). Soon, analytical methods may make it feasible to detect residues at the level of parts per quadrillion, (the equivalent of one centimeter in 10,300,000,000 kilometers (1 inch in 16,000,000,000 miles) or 1 second in 32,000,000 years) which may have the effect of further intensifying public concern because it likely will be possible to detect residues in almost everything. Even though technology permits the detection of these extremely small quantities, such findings do not mean that pesticide residues detected at these levels have any significance in terms of health or environment.

The response to media events, such as the finding of Alar (daminozide) residues on apples in the United States, demonstrates that most people are unaware of these facts and illustrates the almost universal and erroneous belief that all pesticides, at any

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level, are bad. The general public's fear of any detectable amount of pesticide residue, however, is seldom justified by the scientific data.

Biological Testing of Pesticide Residues in Tobacco

There are no persuasive studies that establish scientifically that pesticide residues, as they occur in cigarette smoke, cause lung cancer or other diseases in humans. In fact, after decades of research, inhalation studies in which animals have been exposed to fresh whole tobacco smoke have failed to provide experimental proof that smoking causes lung cancer.[14] The reference or model cigarettes used in these animal studies were made from the same inventories of tobacco used in manufacturing commercial cigarettes which would have contained residues of pesticides also found in food and other retail consumer products. In effect, then, pesticides commonly used on tobacco and other crops have been tested in animals by chronic smoke inhalation studies.

In addition, a research project sponsored by the U.S. government's Tobacco Working Group specifically investigated the effects of pesticides in tobacco smoke condensate. This study compared the biological activity of cigarette smoke condensate from specially grown pesticide-free tobacco with smoke condensate

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from experimental cigarettes grown with commonly used pesticides. The results showed no statistically significant differences between the biological activity of smoke condensate from the pesticide-free compared to the pesticide-treated tobacco.[1-3]

In summary, a comprehensive evaluation of the detectable residues in the cigarette smoke to which the smoker is exposed, the toxicological characteristics of a particular pesticide, and the results of experimental tests with cigarette smoke that contains pesticide residues does not establish a scientific basis for claims that pesticide residues in tobacco contribute to the health risks which have been associated with smoking.

Conclusion

The use of approved pesticides is necessary to achieve efficient and cost-effective production for the farmer and, ultimately, an affordable product for the consumer. Pesticide residues in agricultural products are an unavoidable by-product of the widespread use of pesticides by farmers. Compared to naturally-occurring pesticides in plants, "synthetic" pesticides constitute only a tiny fraction of the chemicals to which humans are exposed in their daily diets. There are no persuasive scientific studies which establish that the very small amounts of pesticide residues

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that have been detected in cigarette smoke are a cause of disease in smokers.

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PESTICIDES

CLAIMS/RESPONSES

CLAIM: Cigarette manufacturers use tobacco which contains pesticides that are harmful to smokers.

RESPONSE: Pesticides are widely used in the production of farm crops throughout the world, because these chemicals help control insects, weeds, and other pests that cause substantial losses. Consequently, small amounts of residues from these substances are found in virtually all the food we eat. Pesticides used in growing these food commodities are also used in growing tobacco.

There are no persuasive scientific studies which establish that the small amounts of residues that have been detected in tobacco products are a cause of disease in smokers.[1-3] In fact, after decades of research, inhalation studies in which animals have been exposed to fresh whole tobacco smoke have failed to provide experimental proof that smoking causes lung cancer.[4] The reference or model cigarettes used in those animal studies were made from the same tobacco used to make commercial cigarettes which would have contained residues of pesticides also found in food and other consumer products. In effect, then, many pesticides commonly used on tobacco and other crops

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have been tested in animals by chronic smoke inhalation studies and have not been scientifically demonstrated to be cause lung cancer.

Furthermore, in response to environmental and health concerns, many governments extensively regulate pesticide use. These regulations are designed to assure that pesticide residues present in food products and other consumables occur at levels which will not result in harm to the consumer.

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CLAIM: Pesticides must be harmful, regardless of how little there is in a product. Why else would the media pay so much attention to reports that there are pesticides in food?

RESPONSE: Technological developments have made it possible to detect extremely small residues of pesticides that were virtually undetectable only a few years ago. However, simply because it is possible to detect small amounts of a substance in, for example, a food product does not establish that it is hazardous. The mechanism that makes pesticides effective in controlling various pests and weeds does not automatically translate into health concerns or an adverse impact on the environment. Orchestrated events such as the "Alar scare" in the U.S. suggest that the media may report the news before all scientific facts have been considered.

In this regard, it is worth considering that nature is the major source of plant defense chemicals. Grain, fruit, and vegetable plants have protective mechanisms that produce chemical defenses against infestation by insects, fungi and animal predators. It has been estimated, for example, that an average American may consume about 10,000 times more natural "pesticides" per day than synthetic or man-made pesticide residues. In

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other words, 99.9% of the pesticide chemicals consumed through the diet are naturally occurring.[1]

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CORONARY HEART DISEASE: EXECUTIVE SUMMARY

Based primarily on statistical reports, claims are often made that cigarette smoking is a major cause of coronary heart disease (CHD), which occurs when the heart does not receive enough oxygen. Despite such allegations, however, a careful review of the literature on CHD demonstrates that the causes of CHD are still not well understood. This literature also demonstrates that there is much that is unknown about what role, if any, smoking may play in its development. In fact, when the literature on tobacco and CHD is critically reviewed, a number of perplexing and unresolved paradoxes surface. For example, smoking is only one of many statistical associations, termed "risk factors," that have been reported for heart disease. Moreover, reductions in such risk factors have not been demonstrated to lead to corresponding reductions in heart disease mortality rates. In addition, there are a variety of inconsistencies and anomalies in the statistical studies of smoking and CHD. Finally, scientists have not been able to establish what, if anything, in cigarette smoke is related to the development of CHD. Accordingly, it is readily apparent that cigarette smoking has not been proven to cause CHD.

The claim that smoking is a risk factor for CHD refers to reports that smokers have a statistically increased risk of the disease. However, it is important not to confuse risk factors with causal factors because, among other reasons, statistical associations cannot provide information on biological processes

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whereby a factor, such as smoking, might lead to heart disease. Thus, such associations, by themselves, cannot establish a causal relationship.

Furthermore, smoking is only one of hundreds of other factors that have been reported to be statistically related to CHD. A few of the most well-known of these include gender (males are more likely to develop CHD than females), genetics, elevated blood levels of cholesterol, high blood pressure, diet, obesity, physical inactivity and stress. Additional risk factors continue to appear in the literature. Yet, which, if any, of these may have causal significance is not known. Certainly, however, there is reason to question their significance in view of the failure of so-called intervention trials to demonstrate that reductions in levels of risk factors, including smoking, lead to reductions in CHD mortality risk.

There are also notable inconsistencies and anomalies in many of the studies reporting associations of smoking and CHD, again, calling into question the claim that smoking causes CHD. For example, some studies, particularly those of women, do not even report a statistical relationship between smoking and CHD. Others indicate that any statistical relationship between smoking and heart disease may be observable only in groups with a high fat or cholesterol intake. It is also a statistical paradox that trends in CHD rates over time are sometimes reported to be inconsistent

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with trends in cigarette smoking. In recent decades, for example, trends in CHD rates have been reported to be increasing in some countries and decreasing in others, apparently with little or no relationship to changes in smoking.

Claims that smoking causes CHD often rely strongly on still other reports that quitting smoking reduces the risk for this disease. It is important to recognize that comparisons of the CHD rates of smokers and exsmokers would be valid only if it were assumed that these groups were the same in all respects except for their smoking habits. This assumption is false, however, as demonstrated by studies from a variety of countries, including Britain, the United States, Japan, and Finland, which report that exsmokers differ from smokers in fundamental, even possibly genetic, ways. In fact, these studies suggest that exsmokers tend to be more like nonsmokers even before they quit smoking.

Finally, the claim is sometimes made that certain constituents in cigarette smoke, specifically carbon monoxide (CO) and nicotine, have adverse effects on the cardiovascular system. Various theories have been discussed about how these substances could exert an effect. However, despite the intensive research to which tobacco smoke has been subjected over many years, these constituents, as found in cigarette smoke, have not been scientifically proven to cause CHD.

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In conclusion, many questions and paradoxes remain unanswered about the possible nature of the role, if any, that smoking may have in the development of CHD. These paradoxes reflect a challenge that only continued research can resolve. Perhaps what is most apparent from the literature is that the causes of heart disease are likely to be numerous and complicated, and that claims focusing on a single factor, such as smoking, should be regarded with considerable skepticism.

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CORONARY HEART DISEASE

Heart disease is one of the leading causes of death in many countries and, perhaps as a result, it has been the subject of intensive scientific study for many years. Although much has been learned during this time, the causes of heart disease are not known. Nevertheless, based primarily on statistical reports, claims are often made that cigarette smoking is a major cause of diseases of the heart, in particular coronary heart disease (CHD), which occurs when the heart does not receive enough oxygen.

Despite such allegations, the literature on CHD demonstrates that there is much that is unknown about what role, if any, smoking may play in its development. In fact, a group of United States physicians recently concluded that when the literature on tobacco and CHD is reviewed critically, "a number of perplexing and as yet unresolved paradoxes painfully surface."[1] For example, although not generally mentioned by anti-smokers, cigarette smoking is only one of many statistical associations, termed "risk factors," that have been reported for heart disease. Others frequently discussed are high blood pressure and elevated blood cholesterol levels. Nor is it generally mentioned by anti-smokers that reductions in such risk factors have not been demonstrated to lead to corresponding reductions in heart disease mortality rates. In addition, there are numerous inconsistencies and anomalies in the epidemiological (population or statistical) studies of smoking and

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CHD. Finally, scientists have not been able to establish what, if anything, in cigarette smoke is related to the development of CHD. Accordingly, it is readily apparent that cigarette smoking has not been proven to cause CHD.

Risk Factors

Smoking is often regarded as a risk factor for CHD because smokers are reported to have a statistically increased risk of the disease. However, risk factors do not necessarily imply cause-and-effect. As a literature review from the University of Oslo, Norway, pointed out, "risk factors should not be confused with causal factors."[2] That is because, among other reasons, statistical associations cannot provide information on biological processes whereby a factor, such as smoking, might lead to heart disease.

Most investigators seem to be aware of the limitations of statistical data. Even reports of the United States Surgeon General have recognized this. For example, the first such report, in 1964, noted that "statistical methods cannot establish proof of a causal relationship in an association."[3] Similarly, in the context of discussing smoking and cardiovascular disease, the 1979 report noted that "correlation [association is a type of correlation] is not synonymous with causation."[4] This basic tenet of scientific interpretation, though widely understood, sometimes

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seems to be forgotten by antismoking advocates when assessing statistical data concerning smoking and CHD.

It is also important to recognize that smoking is only one of literally hundreds of factors that have been reported to be statistically related to CHD. Some of the most well-known of these, in addition to cigarette smoking, high blood pressure, and elevated blood cholesterol levels, are gender (males are more likely to develop CHD than females), genetics, obesity, physical inactivity, and stress. However, these are only a few of the risk factors that have been reported in the literature, and additional risk factors continue to be reported. One major survey in 1981 listed nearly 250 factors that had been reported to be related to CHD up to that time.[5] An updated review in 1986 noted that an additional 30 to 40 risk factors had been reported since the earlier review and that the literature on risk factors "seems to expand at almost an exponential rate."[6] Although these authors consider smoking to be one of the most important risk factors, whether or which of these may have causal significance is unknown, as the following discussion illustrates.

Genetics

One of the most widely discussed CHD risk factors is genetics or heredity. A number of researchers have speculated that this factor may explain why CHD rates tend to be higher in

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certain families, geographic areas and ethnic groups. The potential role of genetics was considered in detail in two major literature reviews by Drs. Neufeld and Goldbourt, scientists at Israel's Tel Aviv University. In their first review published in 1983, they noted that variations in risk factors, including smoking, could not satisfactorily account for differences in CHD rates in different groups but that genetics play a "significant" role "in determining the degree, time course and severity of the atherosclerotic process and the occurrence of symptomatic CHD."[7] In their second review published three years later, they focused on the genetic aspects of atherosclerosis, a narrowing of the arteries which is often an important underlying condition in the development of CHD. Although they cautioned that "speculations still exceed concrete knowledge" about this disease process, they nevertheless emphasized that genetics is given a potentially important role in its development in the literature.[8]

The apparent importance of genetics in CHD development was also emphasized by the late Philip R.J. Burch, an eminent medical physicist from the United Kingdom's University of Leeds. Based on his analysis of data from several major types of epidemiological studies, he concluded that none of these studies "endorses the idea that the classical 'risk factors' -- except, of course, the familial (genetic) one -- exert any appreciable causal action. Claims to the contrary are based on uncritical evidence and faulty logic."[9]

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Stress and Personality

Many studies suggest that people with a certain type of personality are prime candidates for developing CHD. Such persons tend to be hard-driving, time-conscious, often impatient and emotionally tense, characteristics that are likely to promote a stressful lifestyle. No one knows why some persons have such a personality, although it has been speculated that it may have to do with personal preference or some relatively unalterable trait that they are born with. For whatever reason, in most industrialized countries which tend to have the highest CHD rates, many people lead very stressful lives.

One of the most widely discussed aspects of personality in relation to heart disease is the so-called type A versus type B behavior pattern. The pioneers in researching this concept are Drs. Meyer Friedman and Ray Rosenman, who brought these behavior patterns to the attention of the medical community in a 1959 report in the Journal of the American Medical Association. On the basis of their research, they characterized persons with a "type A" behavior pattern as very achievement-oriented, usually toward poorly defined goals, constantly busy, always feeling a sense of urgency about time, alertness and a desire for recognition and advancement. Persons with a "type B" behavior pattern, on the other hand, were generally characterized as having a relative absence of these

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characteristics. When Friedman and Rosenman compared the CHD rates of men with "type A" versus "type B" behavior patterns, they found a "startling difference." Men with "type A" behavior were seven times more likely to have heart disease than men with "type B."[10]

Since its introduction, the "type A" concept has been extensively studied and refined by many researchers and investigators. Friedman argues that their findings have strongly confirmed the role of this behavior pattern in CHD.[11] Much of the recent literature in this area has focused on more specific personality and stress-related characteristics that might be part of a broad personality type such as "type A" or "type B." For example, researchers have reported that "hostility,"[12] "time urgency"[13] and "severe anxiety"[14] are associated with CHD.

Reports of what patients say they are experiencing at the time they have a heart attack are consistent with the epidemiological literature associating CHD with personality and stress. For example, an intriguing clinical study from the United States reported that mental stress may, in fact, act as a potential trigger for a heart attack. When nearly 850 heart attack patients were asked about the events that preceded their heart attacks, their most commonly reported potential trigger was "emotional upset."[15]

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A possible relationship between behavioral characteristics and CHD has also been supported by the results of animal research. In the United States, an experiment with monkeys at a North Carolina school of medicine reportedly demonstrated that animals exposed to unstable, stressful social conditions had increased development of coronary artery atherosclerosis. The researchers conducting the experiment concluded that these data were "consistent" with "current hypotheses concerning the role of individual behavioral characteristics in the development of coronary disease in humans."[16] In a subsequent study by this same research group, it was reported that monkeys that were relatively more "reactive" to stress as measured by increases in heart rate developed more atherosclerosis.[17] Some animal research reports have even suggested biological mechanisms that might explain how behavioral or personality factors could lead to CHD. For example, Dr. William Gutstein, of the New York Medical College, has reported that electrical stimulation of those parts of the brain that may be involved in the body's response to stress can damage the arteries and induce atherosclerosis.[18]

Intervention Trials

Additional questions regarding the significance of risk factors are raised by the results of risk factor intervention trials. These trials are a type of epidemiological study in which attempts are made to test the theory that reductions in risk

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factors, including smoking, will lead to reductions in CHD mortality risk. In such a study, an investigator randomly assigns each participant to either an intervention or a control group. Those in the intervention group receive special assistance in lowering their risk factor levels, for example, to reduce smoking. Their subsequent CHD rates are then compared to those in the control group who did not receive any special assistance.

Despite massive and costly research efforts in numerous countries, intervention trials have failed to establish that lowering risk factor levels reduces CHD mortality risk. The largest of these studies was conducted under the auspices of the World Health Organization in five European countries -- the United Kingdom, Belgium, Italy, Poland and Spain.[19] Other large-scale European trials were performed in Norway[20] and England.[21]

The largest effort undertaken in a single country is the United States' Multiple Risk Factor Intervention Trial, known as MRFIT. MRFIT was designed to examine whether reductions in cigarette smoking, high blood pressure and elevated serum cholesterol would reduce the risk of CHD mortality. Although the participants in the study were successful in reducing the levels of these risk factors, the seven-year follow-up failed to demonstrate that reducing these risk factors significantly reduces the chances of dying from coronary heart disease.[22] Even after a

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10-year follow-up, no statistically reliable overall effect on CHD mortality was reported.[23]

Some researchers apparently have had difficulty accepting weaknesses in the intervention trial data. This was a central point in a review of CHD intervention trials by two Irish researchers. James McCormick and Petr Skrabanek, of the University of Dublin, noted that "[d]espite this considerable body of evidence which shows no benefits for intervention, many have interpreted the results as supportive of their wishful thinking."[24] They cited the example of the WHO study which they pointed out showed "no difference" in CHD mortality between the control and the intervention groups, yet the authors attempted to give their reported results public health importance. As McCormick and Skrabanek pointed out, "It would appear that statistical evaluation can be disregarded if it does not support a forgone conclusion."[25]

Viewed together, the risk factor intervention studies represent a variety of different methodologies and study populations. Yet, each one has reported basically similar results -- namely, the failure to demonstrate statistically significant reductions in CHD mortality attributable to reductions in smoking.

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Inconsistencies and Anomalies

There are notable inconsistencies and anomalies in many of the studies reporting associations between smoking and CHD. For example, the potential statistical association is sometimes reported to be weak or not even present; trends in CHD rates are not explained by changes in smoking consumption; and studies of CHD rates in exsmokers have serious methodological flaws.

Weaknesses in Association

Some studies do not even report a statistical relationship between smoking and CHD. In Busselton, Western Australia, for example, a large-scale prospective study reported no significant association between CHD and smoking. Although the authors did report that smoking was associated with some disease or mortality outcomes, nevertheless, they commented that smoking "was unrelated to CVD [cardiovascular disease] and CHD in either men or women."[26]

Studies of women, in particular, have raised questions about a statistical association between smoking and CHD. For example, in a prospective study of women in Gothenburg, Sweden, researchers reportedly found "no significant increased risk" of CHD in smoking women.[27] In the United States, even the Framingham Heart Study, perhaps the largest and most well-known prospective

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epidemiological study of coronary heart disease risk factors, noted a strong gender difference in any CHD/smoking association. That is, while reports from this study have generally argued for the importance of smoking as a CHD risk factor, it also has been reported that, at least for CHD mortality in women, "no significant relationship can be shown."[28] In fact, on the basis of such apparent gender differences, and on other anomalies in the data, a researcher from Harvard University has suggested that the Framingham Heart Study results in general "are inconsistent with the Surgeon General's views about cigarette smoking and coronary heart disease."[29]

The interpretation of the statistical data on smoking and heart disease is further complicated by reports that this relationship may be observable only in groups with a high fat or cholesterol intake. In fact, the editor of an American medical journal dedicated to the study of the diseases and functioning of the heart has argued that an elevated cholesterol level is the most important factor in the development of heart disease. Although he views smoking as having a role in the development of CHD in individuals with high cholesterol levels, he does not consider it to be an "independent" risk factor.[30] To support this opinion, he cited the experience of the Japanese who are well-known for their low rates of heart disease despite their widespread cigarette smoking, and their low fat and cholesterol diet. Others have also cited the Japanese example as suggesting that cigarette smoking is

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"a weak or nonexistent risk factor for heart attack if atherosclerosis from a high cholesterol diet is absent."[31] Obviously, such reported findings must be taken into account in evaluating the literature on smoking and heart disease.

Trends

It is also a statistical paradox that trends in CHD rates over time do not correspond closely with trends in cigarette smoking. In recent decades, for example, CHD rates have reportedly been increasing in some countries and decreasing in others, but such trends have not been shown to be explained by changes in smoking. A report from St. Thomas's Hospital Medical School, in London, for example, observed that since about 1968, CHD mortality has been decreasing in the United States, Canada and some western European countries. However, when these decreases in CHD were compared to changes in fat intake and smoking habits, it was determined that "the change in fat intake rather than smoking habits would appear to be the likely reason for the decline in CHD."[32]

On the other hand, an upward trend in CHD mortality rates was observed in a study of Swedish males during the same time period that their prevalence of smoking decreased. The authors of this study commented that the increase in CHD mortality was apparent in their study, even though "all" the changes in smoking, exercise, and blood pressure treatment that have been used to explain

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decreases in CHD mortality in other countries "also apply to Sweden."[33]

Exsmoker Studies

Claims that smoking causes CHD often rely strongly on reports that quitting smoking reduces the risk for this disease. Such claims rely on the assumption that smokers and exsmokers are the same in all respects except for their smoking habits. This is a false assumption, however, as demonstrated by studies from many countries, including Britain,[34] the United States,[35] Japan[36] and Finland,[37] which show that exsmokers differ from smokers in fundamental, even possibly genetic, ways. In fact, those studies show that exsmokers tend to be more like nonsmokers even before they quit smoking.

Perhaps the most comprehensive examination of the characteristics of exsmokers was conducted as part of a large-scale ongoing research project in the United States involving California members of Kaiser Permanente, a private health care insurance plan. In that study, a large number of traits and characteristics including many believed to be related to the development of heart disease were measured in groups of smokers, nonsmokers and exsmokers before the exsmokers quit. It was reported that "smokers who later quit showed statistically significant differences from smokers who continued smoking, in certain cardiovascular symptoms, social and

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personal characteristics, smoking intensity, and some other traits."[38]

There is disagreement in the scientific world about the significance of the differences between smokers and exsmokers and how those differences should be interpreted. It has been suggested, for example, that the characteristics of exsmokers put them at a decreased risk of CHD even before they quit smoking.[39] Others have suggested that the characteristics which appear to put exsmokers at decreased risk are "compensated for" by others which may put them at higher risk.[40] These sorts of disagreements indicate the need for further research to obtain a better understanding of the differences between smokers and exsmokers and the possible relationship of those differences to CHD.

Carbon Monoxide and Nicotine

The claim is sometimes made that certain constituents in cigarette smoke, specifically carbon monoxide (CO) and nicotine, have adverse effects on the cardiovascular system. Various theories have been discussed about how these substances could exert an effect. It has been speculated, for example, that both these constituents might increase the rate of the development of atherosclerosis or that they may alter the balance of oxygen supply and demand, thus precipitating angina pectoris (heart pain) or a heart attack. However, despite the intense research to which

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tobacco smoke has been subjected over many years, these constituents as found in cigarette smoke have not been scientifically proven to cause coronary heart disease.

Claims that carbon monoxide in cigarette smoke may be involved in the development of CHD have frequently emphasized the early results of a team of Danish researchers.[41] Their research involved exposing rabbits to carbon monoxide for long periods of time and then microscopically examining the arteries to see if any changes had occurred. In their initial studies, they reported vascular changes which they thought were similar to early stages of atherosclerosis in humans. However, when they repeated the experiments (because they thought their initial studies may have been flawed), they were unable to find a toxic effect of carbon monoxide.[42] These and other weaknesses in the data were noted in a subsequent review of a wide variety of literature relating to carbon monoxide from the School of Public Health at the University of Texas Health Science Center, Houston. The review concluded that the concern which has sometimes been expressed about possible effects of CO exposure on the cardiovascular system "is largely unwarranted."[43]

Even the 1983 U.S. Surgeon General's Report, which was the only report to focus exclusively on cardiovascular disease, expressed a number of important reservations about the data on carbon monoxide and nicotine in relation to this disease. For

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example, the Report observed that animal experiments on atherosclerosis and carbon monoxide "must be considered to be unsatisfactory."[44] With regard to nicotine, the Report conceded that "the evidence for and against a primary role for nicotine in the development or acceleration of atherosclerosis is not conclusive."[45] Furthermore, it stated that a "mechanism whereby nicotine can trigger a cardiovascular event is unknown."[46]

Similar conclusions were reached in the United Kingdom by an independent scientific committee in a report to the government. Although the committee report asserted that smoking has adverse health effects and that CO and nicotine may be involved, it nevertheless noted several weaknesses in the literature. For example, the report stated that nicotine, at levels in cigarette smoke, "has not been shown to harm the cardiovascular system in healthy people."[47] Regarding carbon monoxide and heart disease, the report noted that the literature has "not clearly established" that it is a causal factor.[48]

Conclusion

Many questions remain unanswered about the possible nature of the role, if any, that smoking may have in the development of CHD. These questions reflect a challenge that only continued research can resolve. Perhaps what is most apparent from the literature is that the causes of heart disease are likely to be

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numerous and complicated, and that claims focusing on a single factor, such as smoking, should be regarded with considerable skepticism.

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CORONARY HEART DISEASE

CLAIMS/RESPONSES

CLAIM: Smoking causes coronary heart disease.

RESPONSE:

-- Despite many years of extensive research, scientists have not been able to determine what causes heart disease (CHD). Statements that cigarette smoking is a risk factor, meaning that smokers reportedly have a statistically increased risk of CHD, should not be confused with the more difficult question of whether this reflects biological causation. It is a well-known scientific principle that statistical associations alone cannot establish a causal relationship. And, as noted in a literature review from the University of Oslo, Norway, "there is no accepted mechanism indicating how tobacco smoking might possibly enhance CHD."[1]

-- While some studies report that cigarette smoking is statistically related to CHD, the significance of such data is difficult to interpret because, in fact, literally hundreds of factors are said to have this kind of statistical relationship.[2] A few of the

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most well-known of these include male sex, genetics, elevated blood levels of cholesterol, high blood pressure, obesity, diet, physical inactivity and stress. Which, if any, of the hundreds of reported risk factors may have causal significance is unknown.

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CLAIM: Quitting smoking reduces the risk of heart disease.

RESPONSE:

-- Risk factor intervention trials are specifically designed to determine whether decreases in the levels of risk factors, including smoking, reduce the risk of heart disease. Despite massive and costly research efforts, intervention trials have failed to establish that decreases in risk factors lead to reductions in the risk of dying from heart disease.[1] This was a central point in an important review of CHD intervention trials by two researchers at the University of Dublin, who characterized the literature as providing a "considerable body of evidence which shows no benefits for intervention."[2]

-- Claims that quitting smoking reduces the risk for this disease are often based on comparisons of the CHD rates of smokers and exsmokers. Such comparisons would be valid, however, only if it were assumed that these groups were equivalent except for whether they continued to smoke or quit. This assumption is false, as exsmokers reportedly differ from smokers in numerous ways. In fact, they tend to be more like nonsmokers even before they quit smoking.[3]

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Thus, if exsmokers have lower heart disease rates, it may be because of the sorts of people they are, not simply because they quit smoking.[4]

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CLAIM: The statistical evidence is so overwhelming that the inescapable conclusion is that smoking causes CHD.

RESPONSE:

-- Even if the statistical (epidemiological or population) literature were consistent, such data, by their very nature, do not prove cause-and-effect. That is because, among other reasons, statistical data do not provide information on any possible biological -- i.e., causal -- process. Even reports of the United States Surgeon General have recognized this. The first such report, in 1964, noted that "statistical methods cannot establish proof of a causal relationship in an association."[1] Similarly, in the context of discussing smoking and cardiovascular disease, the 1979 report noted that "correlation is not synonymous with causation."[2]

-- There are many inconsistencies in the statistical studies of smoking and CHD. In fact, some research has even failed to observe a statistical relationship.[3] This has been particularly the case in studies of heart disease in women.[4]

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-- Perhaps the most well-known epidemiological study of heart disease risk factors is the Framingham Heart Study in the United States. Interestingly, on the basis of apparent differences between men and women in any CHD/smoking association, and on other inconsistencies in the data, a Harvard University researcher has suggested that the results from this study generally are "inconsistent" with the U.S. Surgeon General's views about cigarette smoking and CHD.[5]

-- It is also a statistical paradox that trends in CHD rates over time do not correspond closely with trends in cigarette smoking. In recent decades, for example, trends in CHD rates have been reported to be increasing in some countries and decreasing in others, but such trends have not been shown to be explained by changes in smoking.[6]

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ENVIRONMENTAL TOBACCO SMOKE

EXPOSURE STUDIES

A REVIEW OF THE LITERATURE

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ETS: A CHARACTERIZATION

- Environmental tobacco smoke (ETS) is an aged and dilute mixture of sidestream smoke (SS), or the smoke from the burning end of the cigarette, and exhaled mainstream smoke (MS), the smoke to which the smoker is exposed.

- ETS differs chemically and physically from both MS and SS. ETS is a dynamic, ever-changing mixture which, as it ages and dissipates, undergoes chemical reactions and physical change. There is no single definable, reproducibly characterizable entity known as ETS.

- Dissipative forces such as air currents and attraction to surfaces influence SS and exhaled MS. Studies indicate that constituents in ETS are hundreds to thousands of times more dilute than either SS or MS. Often, concentrations of ETS constituents fall below detection limits of current scientific measurement devices.

- As ETS ages, a number of physico-chemical changes take place. Matter evaporates from SS particles as they age to ETS. During the aging process, ETS particles coagulate and increase in size. Chemical compounds partition between the gas and

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particle phase of the smoke. (For example, nicotine is found in the particle phase of MS; in fresh SS, most of the nicotine is in the gas phase.) Decay patterns for constituents of ETS vary over time and are dependent upon physical conditions in the environment.

- ETS is not equivalent to either MS or SS. Many studies and reviews employ sidestream/mainstream smoke comparisons, ostensibly to demonstrate the kind and quantity of constituents involved in exposure to ETS. But such comparisons are deceptive and misleading. As two tobacco smoke chemists reported in 1990:[1]

> Although ETS originates from sidestream and exhaled mainstream smoke, the great dilution and other changes which these smoke streams undergo as they form ETS make their properties significantly different from those of ETS. Thus, the sidestream/mainstream ratios quoted in Table 1 can be misleading if used out of context. The important question is not the ratio of sidestream/mainstream but rather what is the concentration of the constituent in the indoor environment and how does it compare to levels from sources other than ETS. Studies based solely on observations of fresh sidestream, or highly and unrealistically concentrated ETS, should take into account the possible differences between these smokes and ETS found in real-life situations.

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- Even the 1986 Report of the Surgeon General on ETS and the 1986 NRC/NAS Report on ETS conceded:

> Comparison of the relative concentrations of various components of SS and MS smoke provides limited insights concerning the toxicological potential of ETS in comparison with active smoking. As described above, SS characteristics, as measured in a chamber, do not represent those of ETS, as inhaled by the non-smoker under nonexperimental conditions.[2]

Similarly, the NAS Report concluded:

> Because the physicochemical nature of ETS, MS, and SS differ, the extrapolation of health effects from studies of MS or of active smokers to nonsmokers exposed to ETS may not be appropriate . . . .[3]

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EXPOSURE TO ETS

- Published studies indicate that nonsmoker exposure to ETS under normal, everyday conditions is minimal. For example, researchers report that there is little difference in ambient levels of carbon monoxide in smoking and nonsmoking areas of workplaces and public places and in homes with and without smokers.[1-6] Other studies indicate that ETS contributes less than half of the total particles in the air of a typical public place.*[7-14] Nicotine is often used as a marker for ETS

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* A paper published in a 1980 issue of Science magazine, in which the authors reported the results of their efforts to measure particles or particulates in the air of smoking and nonsmoking areas, is often cited to support the claim that ETS is a major indoor pollutant. The authors, Repace and Lowrey, contend that the levels of particles they observed in the smoking areas were much higher than in the nonsmoking areas. However, their study results are inconsistent with many others. For example, the average particle count attributed to ETS in their study was from three to twenty times higher than the average levels reported in other studies of office buildings, restaurants and residences.

There are a number of explanations for the authors' apparent overestimation of ETS exposure. First, they selectively sampled environments such as meeting and game rooms, bars and sandwich shops which did not represent normal occupancy conditions and where particulate levels would likely be high regardless of the presence or absence of tobacco smoke. Second, through inappropriate testing methods, they incorrectly assumed all particles in the air arose from ETS. However, as several researchers have noted, ETS typically contributes about one-third of the overall particle levels in indoor spaces. Moreover, particles also are generated by people and their everyday routine activities such as movement and cooking. (Repace, J. and A. Lowrey, "Indoor Air Pollution, Tobacco Smoke and Public Health," Science 208: 464-472, 1980.)

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exposures because it is unique to tobacco smoke. Typical measurements of nicotine range from an exposure equivalent of 1/100 to 1/1000 of one filter cigarette per hour.[15-22] This means that a nonsmoker would have to spend from 100 to 1000 hours in an office, restaurant or public place in order to be exposed to the nicotine equivalent of a single cigarette.

- Studies which have examined ETS constituent levels of nitrosamines, nitrogen oxides and volatile organic compounds (such as benzene**) report minimal contributions to overall ambient air levels in homes, the workplace and public places.[23-36]

** Benzene exposure from ETS is negligible, despite reports to the contrary.[37-38] "Automotive fuel is, by far, the largest, most pervasive source of benzene exposure. In 1989, the U.S. Department of Health and Human Services estimated that 1 billion pounds of benzene were released into the atmosphere from the refueling and operation of approximately 130 million motor vehicles in 1976 [NIEHS, 1989]. This translates into 7.8 pounds of benzene per vehicle per year. In contrast, a pack-per-day smoker would generate approximately 0.008 pounds of benzene per year, assuming that, at most, 0.5 mg of benzene is generated from one cigarette (MS plus SS) [Hoffmann, 1990]. Based on these estimates, an average person is potentially exposed to 1,000 times more ambient benzene from one automobile than from a smoker in a given year." [From: Response of RJR, The U.S. EPA: "ETS: A Guide to Workplace Smoking Policies," October 1, 1990.]

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Questionnaire Reliability:

- All of the epidemiologic studies on the purported association between ETS exposure and disease in nonsmokers rely solely upon questionnaires about exposure, rather than upon actual exposure data.[39-41] Recent studies indicate that questionnaires are an unreliable and inaccurate measure of exposure. Questionnaire responses about exposure vary widely when compared with actual measurements of ETS constituents in the ambient air.[41]

ETS and Radon:

- A theory that suggests that concentrations of radon decay products increase in the presence of tobacco smoke, thus implying an increased risk of lung cancer for the nonsmoker, has been reported in the literature.[42-44] The theory suggests that radon decay products attach to particles (including ETS) in the air, remain suspended, and are subsequently taken up in the lungs of nonsmokers.

- However, actual data indicate that this is not the case.[45-48] It is the unattached, gaseous fraction of radon which determines the dose of radiation to the respiratory tract. According to these data, as dust or particulate levels

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increase, the unattached fraction of radon daughters will decrease, thereby lowering the potential dose of radiation to the lungs.

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DETERMINATION OF DOSE: COTININE

- It has been reported that cotinine, a substance converted from nicotine by the body, can be used as a biological marker to measure nonsmoker exposure to ETS.[1-2] While some reports suggest that cotinine is a reliable marker for total exposure to tobacco smoke, many others do not.[3-12] Researchers have reported that individuals metabolize nicotine in different ways at different times and that elimination rates for cotinine vary among individuals. In addition, recent research indicates that diet may contribute to levels of nicotine and cotinine found in the body, thereby interfering with ambient air exposure levels.[13] Scientists have also noted that different methods of analysis may influence final recorded levels of cotinine.[14] And finally, because cotinine is a metabolite of a gas-phase constituent of ETS, nicotine, cotinine levels do not represent exposures to other constituents of ETS.

- In conclusion, cotinine is not a reliable quantitative measure of ETS exposure. This is because body fluid levels of cotinine cannot be attributed solely to nicotine in ETS, and because body fluid levels of cotinine do not correlate well with actual ambient air exposures to ETS or with ETS constituents other than nicotine. At best, cotinine may be used as a qualitative marker of ambient nicotine exposures.

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DETERMINATION OF DOSE: LUNG RETENTION

- Cotinine is a biologically inactive substance which has not been correlated with ETS constituents retained in the lung. Several researchers have estimated levels of ETS particulate uptake by nonsmokers to approximate 0.02% (two-hundredth of one percent) that of the particulate exposure of an active smoker.[1-4]

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DETERMINATION OF DOSE: MUTAGENS

- Some reports have suggested that the potential toxicity of ETS can be assessed by measuring mutagens in the body fluids of nonsmokers exposed to ETS.[1-3] Mutagens are substances capable of altering the genetic structure of cells. It is suggested that the presence of mutagens in body fluids (e.g. urine) may be an indication that an individual has been exposed to substances capable of inducing cancer.

- Impetus for the theory arises, in part, from studies which report that various constituents of ETS collected through airborne samples are capable of inducing mutations in bacteria.[4-6]

- However, the significance of such reported findings has not been established. Virtually all air samples, whether in the presence or absence of smoking, are mutagenic. Indeed, no substance, including food and natural materials, has been unequivocally shown to be free of carcinogenic and/or mutagenic properties. In addition, it has been reported that sidestream smoke exhibits diminished mutagenic activity as it ages and becomes diluted (i.e., as it becomes ETS).[7]

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- With few exceptions, studies which have compared mutagens in the body fluids of nonsmokers exposed to realistic levels of ETS and nonsmokers not exposed to ETS report no significant difference in mutagenic activity.[8-11]

- The few studies reporting significant increases in urinary mutagenicity among individuals exposed to ETS[1-3] did not employ realistic levels of exposure to ETS, and they did not control adequately for the presence of mutagens in the diet of the study subjects.

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DOSE: OTHER BIOLOGICAL MARKERS

- It has been suggested that sidestream smoke (and by inference, ETS) contains polycyclic aromatic hydrocarbons (PAH), substances which have been designated as carcinogens by various governmental agencies. However, in a series of papers, German researchers report no significant differences in urinary PAH by-products among nonsmokers exposed to ETS and those not exposed.[1-3] Diet was reported to have a profound influence on PAH by-product formation in all study subjects.

- Japanese scientists have reported that individuals exposed to ETS have increased urinary levels of hydroxyproline (HOP), a substance believed to act as a marker for the breakdown of lung tissue.[4] However, German researchers have reported no increase in HOP excretion among either smokers or nonsmokers exposed to ETS.[5]

- It has recently been suggested that DNA adducts can be utilized as biomarkers to assess exposure (dose) to ETS.[6] (An adduct is a product derived from reactions between chemicals and biological material (such as DNA)). Research, however, does not conclusively support this theory; nonsmokers exposed to ETS do not appear to exhibit increased DNA adduct production.[7] Other studies report no increased chromosomal changes in body

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fluids of nonsmokers exposed to ETS.[8-9]

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BIOLOGICAL PLAUSIBILITY

- The argument for the biological plausibility of the role of ETS in disease causation depends upon the simplistic claim that since mainstream (MS) and sidestream (SS) smoke contain carcinogenic substances, so must ETS. However, this analogy is not proved.

- ETS has never been shown to be carcinogenic in any animal species. Only two animal inhalation experiments investigating ETS and lung cancer have been published. Both studies report no meaningful histopathological differences between animals exposed to ETS and those which were not exposed. In a study conducted by the American Health Foundation,[1-3] the investigators exposed one group of hamsters to mainstream smoke and another group to ETS. Animals exposed to mainstream smoke and ETS lived longer than the sham treated controls. The investigators reported that overall there was no marked increase in tumor incidence in animals exposed to either mainstream smoke or ETS after 18 months of exposure. The second study was a 90-day ETS inhalation study of rats and hamsters.[4] Animals were exposed to ETS concentrations 100 times those concentrations encountered by nonsmokers. These researchers reported no histopathological differences between exposed and control animals. Electron microscopy revealed

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pulmonary changes which could be expected to occur under similar exposure conditions with other substances.

- In addition, recent reviews of the literature on suspected pulmonary carcinogens have indicated that none of the individual constituents in sidestream smoke classified as potentially carcinogenic has been found to induce pulmonary cancer via inhalation in experimental animals.[5-6]

- ETS has not be shown to be mutagenic in any animal or cell culture system when tested at realistic levels of exposure (See Section III).

- These points undermine the credibility of the argument for the biological plausibility of ETS in disease causation.

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ETS AND
LUNG CANCER IN NONSMOKERS

VOLUME I

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PRIMARY EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Introduction

Currently, 29 epidemiologic studies examining lung cancer incidence and spousal smoking have been published.[1-29] Tables 1, 2 and 3 list the United States, Asian and European studies, respectively. For purposes of comparison, the relative risks (point estimates) given in the tables are the overall point estimates for spousal smoking reported in the papers. In some cases, the risk in the table was selected from numerous point estimates presented in the paper, based on different definitions of exposure, break-down of the sample by histological type, etc.

Brief synopses and copies of the papers associated with these studies follow this introduction, at Tabs 1 to 29, arranged in chronological order. The copies are highlighted in yellow for useful information and in blue for negative statements.

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United States Studies

Ten of these studies on spousal smoking and lung cancer in nonsmokers (one cohort, nine case-control) were conducted in the United States (Table 1).[3,5,7-9,11,14,16,24,25] **None of the relative risks (RR) for spousal smoking reported in these studies is statistically significant.** The most recently published paper, that by Janerich, et al., is based upon an unpublished dissertation by Luis Varela.[24] The Janerich, et al., paper discusses a subset of Varela's case-control study, and reports no statistically significant increased risk for spousal smoking, workplace exposure, or exposure in social settings. (It does, however, report a statistically significant increased risk for exposure during childhood (see below).) Overall, the Varela study is important because of its large size and appropriate study design.

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Table 1. United States Studies of Spousal Smoking in Women

Study	Risk Estimate(s)	Comment
Garfinkel, 1981	1.27 (95% CI 0.85-1.89) 1.10 (95% CI 0.77-1.61)	Large cohort study; results contrast with Hirayama
Correa, et al., 1983	2.07 (no CI; n.s.)	Extremely small sample size
Buffler, et al., 1984	0.78 (95% CI 0.34-1.81)	
Kabat and Wynder, 1984	not given	No significant differences between cases and controls regarding ETS exposure at home
Garfinkel, et al., 1985	1.23 (95% CI 0.94-1.60)	Numerous odds ratios presented
Wu, et al., 1985	1.2 (95% CI 0.5-3.3)	Adenocarcinoma only
Brownson, et al., 1987	1.68 (95% CI 0.39-2.97)	Hours per day as exposure category; adenocarcinoma only
Humble, et al., 1987	1.8 (95% CI 0.6-5.4)	
Varela, 1987	numerous	No statistically significant point estimate was presented in 73 different measures of spousal smoking
Janerich, et al., 1990	0.93 (95% CI 0.55-1.57)	Published data for subset of Varela, 1987
Kabat, 1990	0.90 (95% CI 0.46-1.76)	Study in progress; surrogate is "exposed in adulthood at home"

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Asian Studies

In contrast, 13 epidemiologic studies on spousal smoking and lung cancer in nonsmokers (one cohort, twelve case-control) have been conducted in China and Japan (hereafter, "Asian studies") (Table 2).[1,4,10,12,15,17,18,20-22,27,28,29] Of this group, several studies report statistically significant relative risks. However, none of the reported relative risks is greater than 2.5; relative risks under 3.0 have been described as "weak" (see Criticisms section in this notebook). Of particular interest is the 1990 paper by Wu-Williams, et al., conducted in northeastern China.[28] This paper reports a statistically significant negative risk associated with ETS exposure. Other factors (particularly indoor air quality) were reported to be associated with an elevated risk of lung cancer in the Wu-Williams, et al., study; such confounders were not always accounted for in the other Asian studies (see section on Confounders in this notebook).

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Table 2. Asian Studies of Spousal Smoking in Women

Study	Point Estimate(s)	Comment
Hirayama, 1981	2.08 (no CI)	Large cohort study; heavily criticized for improper age-standardization and other flaws
Hirayama, 1984	1.45 (90% CI 1.04-2.02)	Further report on above study
Chan and Fung, 1982	not given	Negative association; suggests more "passive smokers" among controls than cases
Lam, W.K., 1985	not given	Unpublished dissertation; suggests that spousal smoking may be associated with peripheral adenocarcinoma
Akiba, et al., 1986	1.5 (90% CI 1.0-2.5)	Study of atom bomb survivors
Gao, et al., 1987	0.9 (95% CI 0.6-1.4)	"Overall exposure" as surrogate
Koo, et al., 1987	1.64 (95% CI 0.87-3.09)	
Lam, T.H., et al., 1987	1.65 (95% CI 1.16-2.35)	
Geng, et al., 1988	2.16 (95% CI 1.03-4.53)	
Inoue and Hirayama, 1988	2.25 (95% CI 0.91-7.10)	Very small sample size
Shimizu, et al., 1988	1.1 (no CI; n.s.)	Reported statistically significant elevated risks for smoking by case's mother or case's husband's father

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Study	Point Estimate(s)	Comment
Sobue, et al., 1990	0.94 (95% CI 0.62-1.40)	
Wu-Williams, et al., 1990	0.7 (95% CI 0.6-0.9)	Point estimate is statistically significantly negative
Liu, et al., 1991	0.77 (95% CI 0.30-1.96)	Presence of at least one smoker in household used as surrogate

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European Studies

Six studies on spousal smoking and nonsmoker lung cancer were conducted in Europe (Table 3).[2,7,13,19,23,26] Statistical significance was reported in two studies, both by the same research group.[2,26] No major cohort study has yet been conducted in Europe. The cohort studied by Gillis, et al., and Hole, et al., although large, has few lung cancer deaths.[7]

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Table 3. European Studies of Spousal Smoking in Women

Study	Risk Estimate	Comment
Trichopoulos, et al., 1981	2.4 (no CI)	Greece; small case-control study; has been heavily criticized
Trichopoulos, et al., 1983	2.4 (no CI) 3.4 (no CI)	Additional cases and controls added since first paper
Gillis, et al., 1984	not given	Scotland; cohort study; very few lung cancer death (4 cases, 4 controls in women)
Hole, et al., 1989	2.41 (95% CI 0.45-12.83)	Continuation of Gillis, et al., 1984
Lee, et al., 1986	1.00 (95% CI 0.37-2.71)	England
Pershagen, et al., 1987	1.2 (95% CI 0.7-2.1)	Sweden
Svensson, et al., 1989	1.2 (95% CI 0.4-2.9)	Sweden; surrogate is "exposure as adult at home or at work"
Kalandidi, et al., 1990	1.92 (95% CI 1.02-3.59)	Greece; related to Trichopoulos study

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Childhood Exposure to ETS and Adult Lung Cancer in Nonsmokers

When the Janerich, et al., paper was published in 1990, the media focused on a single statistically significant risk ratio (OR) reported by the authors, i.e., an estimated OR of 2.07 (95% CI 1.16-3.68) for "household exposure to 25 or more smoker-years during childhood and adolescence."[24] This OR is the only statistically significant estimate out of 13 exposure categories in the paper. A single statistically significant point estimate could have easily occurred by chance alone in a set of analyses this large.

Only a few other studies have included questions concerning exposure to ETS during childhood, i.e., parental smoking.[5,9,11,12,15,23,25,27] Regarding these studies, Ernst Wynder and Geoffrey Kabat wrote in a 1990 publication:

> No consistent association has been reported for lung cancer and exposure to ETS in childhood, which might be expected to exert a greater effect, especially when followed by exposure throughout adulthood. Of course, recall of ETS exposure in childhood is more difficult than recall of such exposure in adulthood.

(Wynder, E.L. and Kabat, G.C., "Environmental Tobacco Smoke and Lung Cancer: A Critical Assessment," Indoor Air Quality, ed. H. Kasuga (Berlin, Heidelberg: Springer-Verlag, 1990): 5-15.)

Table 4 presents the reported risk estimates from the studies (9 to-date) which discuss childhood ETS exposure and lung

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cancer in nonsmokers. The studies are arranged chronologically in the table. The abbreviation "n.s." stands for "not significant."

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Table 4. Childhood Exposure to ETS and Adult Nonsmoker Lung Cancer Risk

Study	Point Estimate	Statistical Significance
Correa, et al., 1983	not given	n.s.
Garfinkel, et al., 1985		
females	0.91 (95% CI 0.74-1.12)	n.s.
Wu, et al., 1985		
females	0.6 (95% CI 0.2-1.7)	n.s.
Akiba, et al., 1986	not given	n.s.
Gao, et al., 1987		
females	1.1 (95% CI 0.7-1.7)	n.s.
Svensson, et al., 1989		
females, father's smoking	0.9 (95% CI 0.4-2.3)	n.s.
females, mother's smoking	3.3 (95% CI 0.5-18.8)	n.s.
Janerich, et al., 1990		
1-24 smoker/yrs exposure	1.09 (95% CI 0.68-1.73)	n.s.
≥ 25 smoker/yrs exposure	2.07 (95% CI 1.16-3.68)	significantly positive
Kabat, et al., 1990		
males	0.73 (95% CI 0.34-1.59)	n.s.
females	1.68 (95% CI 0.86-3.27)	n.s.
Sobue, et al., 1990		
father's smoking	0.60 (95% CI 0.40-0.91)	significantly negative
mother's smoking	1.71 (95% CI 0.95-3.10)	n.s.
other household members	1.13 (95% CI 0.69-1.87)	n.s.

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Exposure to ETS in the Workplace and Lung Cancer in Nonsmokers

The issue of ETS in the workplace is currently a focus of public interest, as evidenced by the 1990 draft Guide to Workplace Smoking Policies prepared by the United States Environmental Protection Agency. This document is based on the EPA's draft risk assessment, which used data from epidemiologic studies which assessed ETS exposure in terms of spousal smoking, not smoking in the workplace.

The current epidemiologic data on workplace exposures to ETS and lung cancer in nonsmokers are reported in eleven studies which examined workplace exposure via questionnaire.[8,9,11,13,17,22-26,28] None of these studies provides adequate support for an increased risk of lung cancer associated with ETS exposure in the workplace. Only one study reports a single marginally statistically significant risk. The point estimates of the studies (in chronological order) are presented in Table 5. (In the table, "n.s." stands for "not significant.")

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Table 5. Exposure to ETS in the Workplace and Lung Cancer Risk in Nonsmokers

Study	Point Estimate	Statistical Significance
Kabat and Wynder, 1984		
males	18/25 cases vs. 11/25 controls	marginally significant
females	26/53 cases vs. 31/53 controls	n.s.
Garfinkel, et al., 1985		
females, 5 yr exposure	0.88 (95% CI 0.66-1.18)	n.s.
females, 25 yr exposure	0.93 (95% CI 0.73-1.18)	n.s.
Wu, et al., 1985		
females	1.3 (95% CI 0.5-3.3)	n.s.
Lee, et al., 1986	several indices	all n.s.
Koo, et al., 1987		
females	several ORs	all n.s.
Shimizu, et al., 1988		
females	1.2 (no CI given)	n.s.
Svensson, et al., 1989		
females, at home or at work	1.2 (95% CI 0.4-2.9)	n.s.
females, at home and at work	2.1 (95% CI 0.6-8.1)	n.s.
Janerich, et al., 1990		
150 person/yrs exposure	0.91 (95% CI 0.80-1.09)	n.s.
Varela, 1987	27 analyses	all n.s.
Kabat, 1990		
males	0.98 (95% CI 0.46-2.10)	n.s.
females	1.00 (95% CI 0.49-2.06)	n.s.

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Study	Point Estimate	Statistical Significance
Kalandidi, et al., 1990 females	1.08 (95% CI 0.24-4.87)	n.s.
Wu-Williams, et al., 1990 females	1.1 (95% CI 0.9-1.6)	n.s.

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OTHER STUDIES DISCUSSING LUNG CANCER

In addition to the primary lung cancer studies discussed in Section A of this notebook, there are several other studies which are sometimes mentioned in the context of epidemiologic studies on ETS and lung cancer. Because these studies are methodologically flawed or report incomplete data, they are of limited usefulness. For instance, the earlier studies (e.g., Knoth, et al., 1983; Miller, 1984; Sandler, et al., 1985) were excluded from the Letzel and Überla meta-analysis (1990), and even from the meta-analyses conducted by the National Academy of Sciences in 1986 and by the Environmental Protection Agency in 1990.

Following are brief summaries of each of these studies, focusing on their problems. Copies of these studies follow this introduction, arranged in chronological order and highlighted in yellow for useful information and in blue for adverse information.

Knoth, et al., 1983.

- This German study included a total of 792 lung cancer patients. There was no control population for comparison, and thus, the authors' conclusions are of limited value.[1]

- One reviewer commented that this report contained "only tentative conclusions based on poor data analyzed by

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unacceptable methods."[2]

Sandler, et al., 1985

- Although the papers published by Sandler, et al., in 1985 focused on overall mortality, some numbers of lung cancer deaths were presented.[3]

- The methodology and interpretation of these studies have been heavily criticized (e.g., one scientist described the studies as "heavily flawed").[4] The data presented are of limited value.

Dalager, et al., 1986.

- Data from three case-control studies conducted in the United States under the auspices of the National Cancer Institute were combined and analyzed in this study.[5] (Two of the studies, Correa, et al., and Buffler, et al., were discussed in Section A of this notebook.)

- Because the Dalager paper includes two primary studies on ETS and lung cancer, if it were included in considerations of the epidemiologic studies, it would result in some data being "counted" twice.

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Lloyd, et al., 1986.

- In a study investigating the high rate of lung cancer in one town in Scotland, relatives of 42 cases who had died of lung cancer and of 42 matched controls who had died of other causes were interviewed.[6]

- Conclusions about ETS exposure were based on smokers and nonsmokers combined, thus precluding comparisons to the primary studies cited in Section A of this notebook. However, the authors reported no statistically significant differences between cases and controls for any questions relative to personal smoking or to ETS.

Katada, et al., 1988.

- This study, using hospitalized individuals in Nara, Japan, included only 25 female lung cancer cases (some of whom were smokers) and 50 female controls.[7]

- All of the cases reported present exposure to ETS, all but two reported past exposure, and all but four reported childhood exposure. Thus, the reference categories (i.e., non-exposed women) are too small to allow appropriate calculations of relative risk.

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- Nevertheless, none of the case-control comparisons was statistically significant at the 5% level. (Note: the paper also bases some of its conclusions on nonsmokers and smokers combined.)

Lam and Cheng, 1988

- This paper reviews four lung cancer studies previously conducted in Hong Kong, all of which are presented in the Primary Studies section of this notebook.[8]

- Using meta-analysis, Lam and Cheng calculate a statistically significant summary point estimate for the four studies.

Chen, et al., 1990

- In 1990, conclusions based on a study of 332 cases and 635 group-matched hospital controls in Taiwan were published.[9]

- For ETS exposure, point estimates achieving statistical significance were reported; however, it appears that these point estimates were calculated using both nonsmokers and active smokers, and are thus not comparable with other studies of nonsmokers only.

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Miller, 1990.

- Miller used newspaper death notices to ascertain cancer deaths in women in northwestern Pennsylvania, and then interviewed surviving next-of-kin to obtain information on the deceased women. This approach could be expected to result in problems related to accurate recall by those interviewed.[10]

- In a 1984 paper, Miller examined "all cancer deaths" (See Other Cancers section in this notebook); in the 1990 paper, he provides numbers of cancer deaths by site.

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ETS AND
LUNG CANCER IN NONSMOKERS

VOLUME II

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CRITICISMS OF THE EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Some general criticisms are applicable to the majority of the epidemiologic studies on ETS and lung cancer.

Strength of the association

- Wynder and Kabat wrote in 1990:

> An association is generally considered weak if the odds ratio is under 3.0 and particularly when it is under 2.0, as is the case in the relationship of ETS and lung cancer.[1]

Such a weak association calls for special attention to possible sources of bias and confounding.

Exposure bias

- Spouses, next-of-kin or friends are sometimes asked to estimate the amount of ETS to which they think the subject was exposed. This may result in something called "exposure bias" or "exposure misclassification."[2]

- Exposure indices and risk estimates based on this type of information may be improper and incorrect.

- One example of this was reported in the Garfinkel, et al., study, published in 1985, which reported relative risks of 0.83 when the cases answered questions about ETS, 0.77 when

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the cases' husbands answered, and 3.57 when the cases' children answered (a copy of this study may be found in Section A of this notebook).

Reporting bias

- Another type of bias that may arise is "reporting bias," which may result if cases and controls respond differently to questions about personal smoking and ETS exposure.[2]

Publication bias

- "Publication bias" arises from the apparent failure by scientific journals to publish papers reporting negative or weakly positive results. If this occurs, the set of published investigations may not be truly representative of all the studies in the area.[3]

Confounding factors

- The studies did not always account for possible confounding factors. (This is addressed in more detail in the section in this notebook on confounders.)

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Use of questionnaires

- All of the epidemiologic studies on the purported association between ETS exposure and disease in nonsmokers rely solely upon questionnaires about exposure, rather than upon actual exposure data.[4] Recent studies indicate that questionnaires are an unreliable and inaccurate measure of exposure.

- Questionnaire responses about exposure vary widely when compared with actual measurements of ETS constituents in the ambient air.[5]

Histology

- Lung cancer diagnoses were not always histologically or pathologically verified.[1]

- Also, the histological composition, i.e., the type of lung cancer, differed among studies (in some studies, all histological types were included; in others, some types were excluded).[1]

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"Data-dredging"

- Investigators often examine numerous subgroups of the study population, and may report only those conclusions which fit with their hypothesis.[1] (This is sometimes called "data-dredging.")

Misclassification

- If the personal smoking status of subjects is not accurately classified, it could result in "misclassification bias."

- One critic, Peter Lee, contends that the reported "risks" for nonsmokers are the result of bias caused by a small number of smokers who are reported in the studies as nonsmokers.[6]

Conclusion

German scientist Karl Überla discussed some criticisms of the ETS-lung cancer studies at a recent scientific symposium in Argentina:

> The majority of criteria for a causal connection are not fulfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not adequately excluded, there is no intervention study, significance is only present under special conditions and the biological

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plausibility can be judged controversially.[7]

The eminent statistician Nathan Mantel concluded the following:

> [I]t is unlikely that any epidemiological study has been, or can be, conducted which could permit establishing that the risk of lung cancer has been raised by passive smoking. Whether or not the risk is raised remains to be taken as a matter of faith.[3]

Copies of critical papers, highlighted in yellow for useful information and in blue for adverse statments, are found at Tabs 1-7.

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CRITICISMS OF THE HIRAYAMA STUDY

Numerous criticisms of the Hirayama study have been made.[8-21] They include:

- The age distribution of the sample is not representative of the total Japanese population, particularly for women over the age of 40.[8] When a statistical correction is made for this bias, the increased relative risk reported by Hirayama virtually disappears.

- The appropriateness of Hirayama's standardization of the data by husband's age, rather than by subject's, has been questioned.[9-12] When Kilpatrick re-analyzed the data adjusted by subject's age, the model used by Hirayama was shown to be inappropriate and the reported significantly elevated risk associated with husband's smoking was no longer apparent.

- The Hirayama study was not designed to investigate ETS exposure; it is inappropriate to use it to make conclusions about the hypothesis of an ETS-lung cancer relationship.[8]

- Errors and internal inconsistencies in the data and in risk ratios and confidence intervals have been noted and publicly acknowledged by Hirayama.[13-15]

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- The design of the study has been criticized, e.g., use of death certificates as evidence for lung cancer is unreliable[8]; autopsy or histology results were available for only 11.5% (23 of 200) of the cases[8,16]; use of the smoking status of the subject's husband as a surrogate measure for ETS exposure is not reliable[8,12]; many possible confounding factors were overlooked.[8,17]

It appears that Hirayama has never adequately addressed the criticisms; for instance, his 1990 monograph on the study persists in presenting the same data analyses that have been particularly criticized.[18] In addition, Hirayama has not made his original data available for review.[8,19,20]

A bibliography of the criticisms follows. Copies of selected papers are given at Tabs 8-20. They are highlighted in yellow for useful information and in blue for adverse statements.

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CRITICISMS OF THE TRICHOPOULOS STUDY

Regarding the Trichopoulos, et al., study, the following criticisms have been made:

- In 1990, Letzel and Überla evaluated the quality of ETS-lung cancer studies.[22] Based on possible sources of bias and other problems with study design, they concluded that the Trichopoulos, et al. study, in particular, is "methodologically unacceptable" and is "a textbook example of how a case-control study should not be performed." Furthermore, they reported that this study may strongly influence the outcomes of meta-analyses of the ETS-lung cancer epidemiological studies (e.g., when the Trichopoulos study was included in meta-analyses of all possible case-control study combinations, it appeared in 330 of the 353 significant study combinations).

- Methodologically, the study has been criticized for selecting cases and controls from different hospitals; for excluding patients with adenocarcinoma and with alveolar carcinoma; for the lack of histological or cytological confirmation in 35% of the cases; and for its small sample size.[8,24] According to Überla, the small sample size means that "the statistically 'significant' results of this study may well be artefacts from chance, bias or confounding."[23]

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Copies of the articles referenced above, highlighted in yellow for useful information and in blue for adverse statements are found at Tabs 21-23.

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CONFOUNDING FACTORS

Introduction

According to a 1990 publication by a Swedish scientist, Dr. Ragnar Rylander:

> Studies evaluating the hypothesis of a relationship between exposure to environmental tobacco smoke and lung cancer must take into account other environmental risk or protection factors and the possibility that exposure to environmental tobacco smoke may be confounded. This has not been done in the majority of such studies. Until this has been done, the claim of causality between environmental tobacco smoke and lung cancer remains uncertain. [Emphasis added.][1]

In epidemiologic studies, confounders are variables which can affect the outcome of interest, independently of the factor under investigation. Potential confounding factors in studies of ETS and lung cancer are numerous and varied.[2] It is difficult to control for all of them in the design of an epidemiologic study. Following are lists of some of the possible confounders encountered in epidemiologic studies of lung cancer incidence in nonsmokers, both those specifically considering ETS and those dealing with other factors.

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Heating and Cooking Fuels

- In developing countries, the use of certain fuels (kerosene, gas, coal, liquefied petroleum gas, straw, or wood) for heating and cooking contributes to elevated levels of indoor air pollution, which may contribute to disease incidence.[3]

- Following earlier, limited reports[4] on exposures to fumes from the use of various fuels, eight studies examining coal use in stoves and other indigenous heating devices in China have recently been published.[5-12] RRs as high as 14 have been reported,[8] although most RRs are in the 1.0 to 2.0 range.[11,12]

- Some fuels, namely, kerosene or coal and wood or straw, have been associated with a increased risk of lung cancer in Japanese women as well.[13,14]

Cooking Techniques

- The use of certain cooking oils and some cooking techniques (i.e, stir-frying and deep frying) which produce oil vapors have been associated with increased lung cancer risks in Chinese women.[11,15]

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Air Pollution

- In addition to indoor air pollution from heating and cooking fuels, as described above, outdoor air pollution has been associated with increased lung cancer incidence in at least one epidemiologic study in northeast China.[12]

Dietary Factors

- Increased lung cancer risk has been associated with the consumption of smoked, salted, cured, pickled, processed, or spicy foods among Oriental women.[18] Additionally, research suggests that wives whose husbands smoke may consume more processed and spicy foods and eat fewer fresh fruits and vegetables than do those whose husbands do not smoke.

- One study reported an elevated lung cancer risk among Oriental women associated with the consumption of green or black tea.[17]

- It has also been reported that nonsmokers married to smokers have lower intakes of dietary carotene, a substance associated with decreased cancer risks when consumed in sufficient amounts.[18] Recently, an abstract reported an correlation between serum carotene levels and socioeconomic status; this

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could be important if smoking and SES are also correlated, as has been suggested.

Occupation

- Some of the studies considering lung cancer in nonsmokers have also reported elevated relative risks associated with employment in certain fields or with occupational exposures to certain substances.[5,11-13]

Medical and Lifestyle Factors

- Personal health factors such as menstrual cycle length and previous history of respiratory disease (including tuberculosis, pneumonia or emphysema) have been associated with increased risk for lung cancer.[5,9,11,15]

- Family history of lung cancer has also been associated with increased lung cancer risk.[9,11]

- An association between husband's smoking status and family lifestyle has been reported.[16] Wives with husbands who were nonsmokers had better SES, were more conscientious housewives, ate better diets, had higher indices of family cohesiveness,

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and had better indices of overall health than did women married to smokers.

- At least one hobby, keeping pet birds, has been associated with increased lung cancer risk.[19]

Conclusion

While of general importance, the question of confounders appears to be particularly relevant in studies of Asian women. Certain cultural variables (e.g., use of smoky fuels, certain cooking methods, diet) differ greatly between Asian and Western populations. The potential effects of such factors must be considered when evaluating the results of epidemiologic studies on lung cancer incidence, particularly those considering ETS exposure. Table 1 presents a comparison and summary of Asian studies to date, revealing the increasing attention paid to confounders in these studies.

Dr. Linda Koo, in her 1988 paper on lifestyle correlates, summed up the importance of confounders as follows:

> [C]aution should be exercised when interpreting data on ETS. It may not be the hazards of tobacco smoke that are being evaluated, but a whole range of behaviors that result from having a smoking husband, which may in turn increase the risk for certain diseases among their wives and children.[16]

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Table 1a. Asian Studies Included in EPA Draft Risk Assessment: Epidemiologic Studies of Lung Cancer in Nonsmoking Women, with Spousal Smoking Included

Study [site]	Sample Size	Spousal Smoking*	Factors Considered: Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
Hirayama, 1981, 1984 [Japan]	91,540	(+)	--	--	--	--
Chan and Fung, 1982 [Hong Kong]	223	(-)	--	Yes	--	--
Lam, 1985 [Hong Kong]	248	(-)	--	Yes	--	Home incense burning
Akiba, et al., 1986 [Japan]	1,385	(+)	--	--	--	Radiation exposure
Gao, et al., 1987 [Shanghai]	1,407	(-)	--	Yes	Yes	Medical history; hormonal factors
Koo, et al., 1987 [Hong Kong]	225	(-)	--	--	--	--
Lam, et al., 1987 [Hong Kong]	890	(+)	--	--	--	--
Geng, et al., 1988 [Tianjin, China]	314	(+)	Yes	--	--	Medical history; occupation
Inoue and Hirayama, 1988 [Japan]	83	(+)	--	--	--	--

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Study [site]	Sample Size	Spousal Smoking*	Factors Considered: Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
Shimizu, et al., 1988 [Japan]	180	(-)	Yes	--	Yes	Occupation

* (+) indicates a statistically significant relative risk was reported; (-) indicates the reported relative risk was not statistically significant.

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Table 1b. Asian Studies Published After EPA Draft Risk Assessment: Epidemiologic Studies of Lung Cancer in Nonsmoking Women, with Spousal Smoking Included

Study [site]	Sample Size	Factors Considered: Spousal Smoking*	Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
He, et al., 1990 [China]	536+	(-)	Yes	Yes	--	Medical history
Sobue, et al., 1990 [Japan]	639	(-)	Yes	--	--	--
Wang, et al., 1990 [NE China]	110	(-)	Yes	--	--	Indoor and outdoor air pollution
Wu-Williams, et al., 1990 [NE China]	1,924	(+)**	Yes	Yes	Yes	Medical history; occupation
Liu, et al., 1991*** [China]	221	(-)	Yes	Yes	--	Medical history

* (+) indicates a statistically significant relative risk was reported; (-) indicates the reported risk was not statistically significant.
\+ Males and females combined.
** The reported relative risk was statistically significantly negative.
***Full report on population discussed in He, et al., abstract.

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Table 1c. Ancillary Asian Studies, Not Considered in EPA Draft Risk Assessment

Study [site]	Sample Size	Factors Considered: Spousal Smoking	Heating Methods/ Fuel Use	Cooking Tech-Niques	Diet	Other
Koo, et al., 1984 [Hong Kong]	400	No**	--	--	--	--
Mumford, et al., 1987 [China]	--	No	Yes	--	--	--
Chapman, et al., 1988 [China]	144+	No	Yes	--	--	--
Koo, et al., 1988 [Hong Kong]	136	No	--	--	Yes	Lifestyle variables
Du and Ou, 1990 [China]	1,324	No	Yes	--	--	--
Xu, et al., 1990 [NE China]	1,077	No	Yes	Yes	Yes	Indoor and outdoor air pollution; occupation

** Other questions were asked regarding ETS.
+ Males and females combined.

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A selection of the relevant literature follows. Useful information is highlighted in yellow; problematic statements are highlighted in blue.

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USE OF META-ANALYSIS: EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

Introduction

The statistical procedure of meta-analysis treats the results of individual studies as individual data points in an overall analysis. It has been used effectively in combining the results of randomized, controlled clinical trials of pharmaceuticals. Such studies are eminently comparable because their methodologies and study populations are very similar.

More recently, meta-analysis has been used to analyze the results of epidemiologic studies, that is, to calculate an overall relative risk as a weighted average of the relative risks of many studies. Because of the inherent differences in study design, methodology, and sample population, especially in the case of epidemiologic studies on ETS and lung cancer, questions have been raised regarding the appropriateness of using this procedure to analyze epidemiologic data. However, meta-analysis is still being used; most recently, the U.S. Environmental Protection Agency (EPA) used a meta-analysis to calculate an estimated overall relative risk for lung cancer related to exposure to environmental tobacco smoke (ETS).[1]

The EPA meta-analysis is not the first in this area. The risk estimates calculated by several other meta-analyses are given in Table 1 for comparison.[2-8]

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In addition to its meta-analysis on United States ETS-lung cancer studies, the recent paper by Fleiss and Gross (1991) presents a detailed criticism of the meta-analytical method, particularly as applied to the ETS literature.[8] This is a thorough review paper and a useful reference. Some relevant quotations follow:

> [T]he authors of the NRC report appear not to have followed the major guidelines proposed by Sacks, et al. For example, they did not provide a formal protocol for the meta-analysis, nor, apparently, did they give any consideration to the possibility of heterogeneous ORs across the several studies. (p. 134)
>
> Furthermore, the question comes to mind whether the existing epidemiological studies of a possible association between exposure to ETS and the incidence of lung cancer in non-smokers are of adequate quality. Indeed, there is the question whether any of these studies meets even minimal standards of quality. (pp. 134-135)
>
> There are many reasons for restricting attention to American studies of whether there is an elevated risk of lung cancer to non-smokers exposed to ETS relative to non-smokers not so exposed. One is that this is the population to whom policy decisions will apply and on whom those decisions should be based. (p. 135)
>
> Odds ratios from studies in other countries, on the other hand, are derived from distributions that may differ markedly from those in the U.S., and thus the ORs themselves may not be relevant to the American experience. Genetic and lifestyle differences between the U.S. population and the populations studied elsewhere (mainly in east Asia) also argue for a meta-analysis only of U.S. studies. (p. 135)

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> [U]ncritical use of meta-analysis can and does lead to unsubstantiated conclusions. Only when all the issues that we have discussed are considered and possibly accounted for is it possible to apply meta-analysis so that the overall result is scientifically valid. (p. 137)
>
> It is very unlikely that the biases present in the epidemiological studies of the possible association between exposure to ETS and the risk of lung cancer can ever be removed. The meta-analysis performed by the NRC must either be completely discounted or, as Stein concluded so succinctly in another context, considered a mere 'computational exercise.' (p. 137)

(An editorial comment on this paper by Spitzer is also included.[9])

Copies of some of the referenced articles are included at Tabs 1-4. They are highlighted in yellow for useful information, and in blue for adverse information.

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Table 1. Results of Meta-Analyses of Epidemiologic Studies of Spousal Smoking and Female Lung Cancer

Meta-Analysis	Summary Risk Estimate	Studies Included
Wald, et al., 1986	1.35 (95% CI 1.19-1.54)	13; 10 case-control, 3 cohort
NRC, 1986	1.32 (95% CI 1.16-1.51)	13; 10 case-control, 3 cohort
Blot and Fraumeni, 1986	1.3 (95% CI 1.1-1.5)	12; 10 case-control, 2 cohort
Wells, 1988	1.44 (95% CI 1.26-1.66)	17; 14 case-control, 3 cohort
EPA, 1990	1.41 (95% CI 1.26-1.57)	22; 19 case-control, 3 cohort
	1.25 (95% CI 1.03-1.52)	8 U.S. studies; 7 case-control, 1 cohort
Letzel and Überla, 1990	1.118 1.076	12; 10 case-control, 2 cohort 11; 9 case-control (Trichopoulos excluded), 2 cohort
Fleiss and Gross, 1991	1.12 (95% CI 0.95-1.30)	9 U.S. studies; 8 case-control, 1 cohort
Layard and LeVois, 1991 (unpublished)	1.08 (95% CI 0.96-1.22)	26; 23 case-control, 3 cohort

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